

## **REMARKS**

Claims 1-96, 99-108 and 111-207 appear in this application for the Examiner's review and consideration. Claims 97, 98, 109 and 110 have been canceled without prejudice solely to expedite the allowance of the remaining claims. Applicants expressly reserve the right to file one or more continuation and/or divisional applications directed to the subject matter of the canceled claims and/or subject matter of the present amendments.

The specification has been amended to correct typographical and/or clerical errors. In particular, support for the amendment to the chemical drawing on page 18, line 1 (and in claim 88) can be found, e.g., at page 33, line 13. Support for the amendment on page 33, line 7-9 can be found, e.g., at page 18, line 1. Claims 1, 16, 17, 21, 42, 60, 88-96, 99-108, 111, 118, 119, 126, 127, 134, 135, 142, 143, 150, 151, 158, 159, 166, 167, 174, 175, 182, 183, 190, 191, 198, 199, 206 and 207 have been amended to correct typographical and/or clerical errors. The amendments to the specification and claims are believed to introduce no new matter. As the application has already published as United States Patent Application Publication No. US 2004/0235853 A1 on November 25, 2004, Applicants believe the submission of a substitute specification containing the current amendments is not required.

Applicants note with appreciation that the Office Action Summary and page 4, item 6 of the Office Action indicate that claims 1-41, 61, 62, 88, 89, 100, 101 and 112-175 are allowed. Applicants further note that claims 44, 46-58, 60 and 176-207 are not rejected but objected to.

Favorable reconsideration of the claims in view of the amendments and remarks herein is respectfully requested.

## **REJECTION OF CLAIMS 42, 43, 45, 59 AND 63 UNDER 35 U.S.C. §103(a)**

On page 2, paragraph 4 of the Office Action, claims 42, 43, 45, 59 and 63 have been rejected under 35 U.S.C. §103(a) as allegedly obvious over the publication of Toldy et al., "Thiocarbamidderivate mit tuberkulostatischer wirkung, II Acylthiocarbamide," *Acta Chemical Academiae Scientarum Hungaricae, Tomus 69*(2):221-227 (1971) ("Toldy II").

The Office Action alleges, on page 3, that Toldy II teaches 4-(6-chloro-3-pyridazinyl)-N-(4-ethoxyphenyl)-1-piperazinecarbothioamide and 4-(6-methoxy-3-pyridazinyl)-N-(4-ethoxyphenyl)-1-piperazinecarbothioamide and that these compounds

are “almost the same as applicants when applicant’s formula (III) has the [following] substituents” given in the Office Action.

Applicants respectfully traverse.

**1. The Legal Standard to Establish a *Prima Facie* Case of Obviousness**

The Examiner has the burden of establishing a *prima facie* case of obviousness by proving three elements: (1) a particular reference (or combined references) must suggest or teach all the limitations of the challenged claim, (2) a suggestion or motivation from the prior art or in the knowledge generally available to one of ordinary skill in the art to modify or combine the reference teachings, and (3) a reasonable expectation of success must exist from the prior art. M.P.E.P. §§2142, 2143, citing *In re Vaeck*, 947 F.2d 488, 493, 20 U.S.P.Q.2d 1438, 1442 (Fed. Cir. 1991). Care must be exercised not to use the applicant’s disclosure to fill in the gaps of the prior art. *In re Vaeck*, 947 F.2d 488, 493, 20 U.S.P.Q.2d 1438, 1442 (Fed. Cir. 1991), citing *In re Dow Chemical Co.*, 837 F.2d 469, 473, 5 U.S.P.Q.2d 1529, 1531 (Fed. Cir. 1988). Further, “[a] prior art reference must be considered in its entirety, i.e., as a whole, including portions that would lead away from the claimed invention.” M.P.E.P. 2141.02(VI) (emphasis in original) (Citing *W.L. Gore & Associates, Inc. v. Garlock*, 721 F.2d 1540 (Fed. Cir. 1983)).

**2. Toldy II Fails to Teach or Suggest Each and Every Claim Element**

Toldy II discloses, in the second paragraph on page 222, that “Alkoxyphenylisothiocyanaten” [i.e., alkoxyphenylisothiocyanates] can be reacted with “N-substituierten Piperazinen” [i.e., N-substituted piperazines] to obtain “Thiocarbamidderivate” [i.e., thiocarbamide derivatives]. The exemplary N-substituted piperazines that are taught in Toldy II are:

- N-carbo-n-propoxypiperazin[e],
- N-carbo-i-propoxypiperazin[e], and
- N-carbo-i-amyoxyypiperazin[e]

(bottom portion of page 225 of Toldy II, section entitled “Verfahren A”). Additional N-substituted piperazines are purportedly provided in Table I of Toldy II (line following “Verfahren A” on page 225 of Toldy II). However, no such table can be found within the boundaries of Toldy II. In contrast, the piperazine moiety of the compounds of, e.g., independent claim 42, is substituted with pyridazine. Because there is no disclosure in Toldy

II of a piperazine that is substituted with pyridazine, Toldy II fails to teach or even suggest all elements of the rejected claim.

Applicants note that an earlier publication in the “Toldy” series, i.e., Solym et al. and Toldy, “Thiokarbamidderivate mit tuberkulostatischer wirkung, I Verbindungen mit heterocyklischem thiokarbamidskelett,” *Acta Chimical Academiae Scientiarum Hungaricae, Tomus 68*(1-2):99-132 (1971) (“Toldy I”) and the English translation thereof, references C32 and C33 respectively in the accompanying Supplemental Information Disclosure Statement, unlike Toldy II, clearly do provide copies of the tables referred to therein. However, missing Table I of Toldy II cannot correspond to Table I of Toldy I because, *inter alia*, the former requires 21 compounds (“I-XXI,” line following “Verfahren A” on page 225 of Toldy II) while the latter provides only 14 compounds (e.g., Table I of reference C33).

Given that there is no Table I in Toldy II, Applicants question the credibility of the English abstract for Toldy II (provided with the present Office Action), which alleges that Toldy II discloses “4-(6-chloro-3-pyridazinyl)-N-(4-ethoxyphenyl)-1-piperazinecarbothioamide” (“compound A”) and “4-(6-methoxy-3-pyridazinyl)-N-(4-ethoxyphenyl)-1-piperazinecarbothioamide” (“compound B”). In any event, the English abstract for Toldy II need not be considered further because, *inter alia*, failing to disclose a method for making compound A and/or compound B, it is not enabling and it cannot render the rejected claims obvious. *Ashland Oil, Inc. v. Delta Resins & Refractories, Inc.*, 776 F.2d 281, 227 U.S.P.Q. 657 (Fed. Cir. 1985), *cert. denied*, 475 U.S. 1017 (1986) (The test whether a particular compound described in the prior art may be relied upon to show obviousness is whether the prior art provided an enabling disclosure with respect to the disclosed compound. Because the evidence showed that a certain compound was a “hypothetical structure,” it was not persuasive of obviousness.)

### **3. Toldy II Teaches Against the Substitution of Piperazine with Substituents Other Than Carbalkoxy Substituents**

A reference may be said to teach away when a person of ordinary skill, upon reading the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicant. *In re Gurley*, 27 F.3d 551, 31 U.S.P.Q.2d 1130 (Fed. Cir. 1994).

As discussed above, Toldy II discloses at page 222 that alkoxyphenylisothiocyanates can be reacted with N-substituted piperazines. Toldy II further discloses at page 222 that most of the resulting thiocarbamide derivatives are inactive (“deren Mehrzahl inaktiv war”),

and that only those thiocarbamide derivatives with a carbalkoxy substituent had activity (Eine Ausnahme bildeten allein jene Verbindungen, die Carbalkoxy-Substituenten enthielten. Unter diesen war das Carbäthoxyderivat VII am aktivsten (6 µg/ml, Dubos)). The compounds of claim 42, however, are substituted with pyridazine. Thus, since Toldy II teaches against the substitution with substituents other than carbalkoxy, Toldy II does not render the claimed compounds obvious. “A prior art reference must be considered in its entirety, i.e., as a whole, including portions that would lead away from the claimed invention.” M.P.E.P. 2141.02(VI) (emphasis in original) (Citing *W.L. Gore & Associates, Inc. v. Garlock*, 721 F.2d 1540 (Fed. Cir. 1983)).

4. **There is no “Rule” that Position Isomers are *Prima Facie* Structurally Obvious**

The Office Action, on page 3, puts forward the proposition that it is “well established that position isomers are *prima facie* structurally obvious even in the absence of a teaching to modify” and cites several historical cases allegedly supporting this proposition. In particular, on page 4 the Office Action proceeds to purportedly quote one of those cases, *In re Mehta*, 146 U.S.P.Q. 284 (C.C.P.A. 1965) (emphasis in original), as follows: “Position isomerism is a fact of close structural similarity.” Applicants respectfully point out that this quote has been truncated and taken out of the context of Mehta; the entire quote is as follows:

Position isomerism is a fact of close structural similarity which is to be taken into consideration with all other relevant facts in applying the test of obviousness under 35 U.S.C. 103.

*In re Mehta*, 146 U.S.P.Q., at 287 (further emphasis added). For the convenience of the Examiner, a copy of *Mehta* is provided in Exhibit 1. It is apparent that a completely different perspective results when this portion of *Mehta* is considered in its entirety. *Mehta* does not stand for the proposition that “position isomers are *prima facie* structurally obvious.” Rather, *Mehta* holds that position isomerism is to be taken into consideration with all other relevant facts in determining whether a claim is obvious.

Put another way, as the Federal Circuit has stated in the context of reversing an obviousness rejection of claimed compounds that were alleged to be so “closely related in structure” to the cited reference compounds as to render the former *prima facie* obvious, “generalization is to be avoided insofar as specific structures are alleged to be *prima facie*

obvious one from the other.” *In re Jones*, 958 F.2d 347, 349-350 (Fed. Cir. 1992) (citation omitted).

On page 4, the Office Action goes on to quote another of the cited cases, *Ex parte Engelhardt*, 208 U.S.P.Q. 343, 349-350 (Bd. Pat. Appeals 1980) as follows: “... position isomerism has been used as a tool to obtain new and useful drugs.” As the issue under consideration in *Engelhardt* was “whether or not one skilled in the pertinent art area would have expected the replacement of the nitrogen atom in the known antidepressant with an unsaturated carbon to produce a compound which would be useful in the treatment of depression” (*Engelhardt*, 208 U.S.P.Q., at 350-351; emphasis added), any pronouncement in *Engelhardt* relating to positional isomerism can be, at most, dicta, not law, as the issue decided in *Engelhardt* does not relate to position isomerism.

##### **5. It is Improper to Read into the Art the Applicants’ Own Teachings**

Moreover and only for the sake of argument, even if the “tool” of position isomerism is to be applied to, hypothetically, compound A, where does the suggestion or motivation to modify the position at which the Cl is substituted (from adjacent or “ortho” to a pyridazine nitrogen to “ortho” to the point where the pyridazine is attached to piperazine) originate? Why not instead modify the position where the Cl is substituted on pyridazine to “meta” to the point where the pyridazine is attached to piperazine? Why not instead modify the position where the pyridazine is substituted on the piperazine ring from 3-pyridazinyl to 4-pyridazinyl? To 5-pyridazinyl? Why not instead modify the position where the ethoxy is substituted on the phenyl ring from 4-ethoxy to 3-ethoxy? To 2-ethoxy? Why not combine more than one of these modifications? Are not any and/or all of these position isomerisms possible? The Office Action does not provide any source for the suggestion or motivation to select only one of these position isomerism modifications and/or which one to select, other than “[s]aid compounds are almost the same as applicants . . .” (Office Action page 3).

As held in *In re Deminski*, a PTO rejection for obviousness is improper when there is nothing in the cited prior art references, either singly or in combination, to suggest the desirability of the claimed subject matter. That the construction in a particular prior art reference would have resulted in the claimed combination had it followed the “common practice” of attaching certain parts does not show obviousness at the time of the invention but rather reflects improper hindsight analysis and the reading into the art of the applicant’s own teachings. *In re Deminski*, 796 F.2d 436, 230 U.S.P.Q. 313 (Fed. Cir. 1986).

Moreover, for any given position isomerism modification or combination of modifications, where does the reasonable expectation of success exist from the prior art? The Office Action does not provide any source for the reasonable expectation of success from the prior art which, in fact, is directed towards antituberculotic activity and not toward, e.g., treating pain pursuant to the title of the present application.

### **CONCLUSION**

Applicants respectfully submit that Toldy II fails to teach or suggest all of the claim limitations, as discussed in detail above. Furthermore, Applicants respectfully submit that there is no suggestion or motivation from the prior art to modify the teachings of Toldy II to include, *inter alia*, a 3-pyridazinyl group substituted with an R<sub>1</sub> group adjacent to the 3-pyridazinyl group's point of attachment to piperazine, as is recited in present independent claim 42. Additionally, even if only for the sake of argument such modifications were to be made, Applicants respectfully submit that Toldy II does not and cannot indicate any reasonable expectation of success to one of ordinary skill in the art in connection with the invention claimed in claim 42 and the claims dependent therefrom.

Accordingly, as the compounds recited in independent claim 42, and claims 43, 45, 59 and 63 dependent therefrom, are not obvious over the teachings of Toldy II for at least these reasons, reconsideration and withdrawal of the rejection relating thereto and early allowance of these claims is respectfully requested.

In view of the foregoing amendments and remarks, Applicants respectfully submit that all of the rejections have been overcome and should be withdrawn. Thus, reconsideration and early allowance of all of the claims are respectfully requested.

Applicants believe that no fee is due in connection with this amendment (other than for the Petition for Extension of Time and Supplemental Information Disclosure Statement submitted separately herewith). However, should the Patent Office determine that a fee is due, please charge the required amount to Jones Day Deposit Account 50-3013.

Respectfully submitted,

*Samuel B. Abrams by  
Gusge A. Smith* 42,140  
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Samuel B. Abrams (Reg. No.)  
**JONES DAY**  
222 East 41st Street  
New York, New York 10017  
(212) 326-3939

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Enclosures